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(54) Title: COMBINATION OF GLUCOSAMINE WITH HERBAL EXTRACTS OF TRIPTERYGIUM, LIGUSTRUM AND ERYCIBE

(57) Abstract: A herbal composition comprises glucosamine and at least one Chinese herb selected from *Tripterygium wilfordii*, *Ligustrum lucidum* and *Erycibe schmidtii*. The herbal composition is useful for alleviating the symptoms of an ailment that involves the inflammation or degeneration of joint tissues, such as arthritis, and can be formulated into a dietary supplement or a pharmaceutical or veterinary composition.

COMBINATION OF GLUCOSAMINE WITH HERBAL EXTRACTS OF TRIPTERYGIUM, LIGUSTRUM AND ERYCIBE

The present invention relates to herbal formulations comprising glucosamine and Chinese herbs which can be administered to humans and animals as dietary supplements and as pharmaceutical dosage forms to alleviate the symptoms of arthritis.

There are more than one hundred forms of arthritis and related conditions. Two of the most prevalent forms are rheumatoid arthritis and osteoarthritis. Both diseases share a common pathology relating to inflammation and tissue destruction (Figure 1). In the affected joint, there develops a downward spiral of (i) inflammation-induced tissue destruction followed by (ii) cytokine release leading to (iii) continued inflammation. This cycle results in a progressively debilitating pathology which manifests as pain and deformity. In healthy individuals there exists a balance between cartilage/proteoglycan synthesis and degradation. In arthritic cartilage, this metabolic balance has deteriorated, despite possible enhanced proteoglycan synthesis, because the rate of degradation exceeds the rate of synthesis. In general, the severity of the disease corresponds with the degree to which degradation exceeds synthesis. Thus, the extracellular matrix of cartilage is destroyed in arthritic patients.

Glucosamine increases the ability of cartilage to synthesize both sulphated mucopolysaccharides and protein in a dose-dependent way, thus restoring the degradation-synthesis balance of cartilage. In one double-blinded, placebo-controlled study of 1208 patients receiving 1500 mg oral glucosamine daily for fifty days, the symptoms of pain at rest, on standing, on exercise and during limited active and passive movements improved steadily through the treatment period. The improvement obtained lasted for a period of six to twelve weeks after the end of treatment. Objective therapeutic efficacy was rated by the doctors as good in 59% of patients, and sufficient in an additional 36% of patients. Tapadinhas, M.J. et al., *Oral glucosamine sulphate in the management of arthritis: report on a multi-center open investigation in Portugal,* 3 PHARMATHERAPEUTICA 157-168 (1982). Oral glucosamine was fully tolerated by 86% of patients, a significantly larger proportion than that reported with other treatments and approached only by injectable glucosamine.

Today, glucosamine is available in America and European countries as a dietary supplement in the form of tablets, capsules and chewable bars containing pharmaceutical grade glucosamine. For example, pure commercial glucosamine products are available containing

glucosamine sulphate in 500 mg capsules or in 750 mg capsules. Combinations of glucosamine with herbs, vitamins and minerals are also available; an example of a commercially available product contains glucosamine (300 mg), chondroitin sulfate, ginger, white willow, boswellia, curcumin, vitamin C, zinc, manganese, and selenium.

Other formulations of glucosamine include those described in U.S. Patent 5,679,344 to Williams et al. (Oct. 21, 1997), which provides glucosamine and anti-inflammatory proteolytic enzyme(s). However, this formulation only modulates the absorption of the glucosamine from the digestive tract and does not modulate the immune response which underlies the deterioration of the affected joint. Another composition of glucosamine and an anti-inflammatory agent is described in U.S. Patent 5,843,919 to Burger (Dec. 1, 1998). The anti-inflammatory agent in this patent is any fatty acid of the group of omega-3-fatty acids which is thought to inhibit the synthesis of prostaglandins that regulate inflammation in mammals. The glucosamine-based herbal compositions that currently exist generally provide nominal amounts of such untested anti-inflammatory ingredients.

While glucosamine is generally accepted as being effective and safe for treating osteoarthritis, medical intervention into the treatment of this degenerative joint diseases is generally restricted to the alleviation of its acute symptoms. Medical practitioners generally use nonsteroidal and steroidal anti-inflammatory drugs for treatment of osteoarthritis. These drugs, however, are not well-adapted for long-term therapy because they not only lack the ability to promote and protect cartilage, they can actually lead to degeneration of cartilage or reduction of its synthesis. Moreover, most nonsteroidal anti-inflammatory drugs damage the gastrointestinal system when used for extended periods of time. Thus, new treatments for arthritis are urgently needed.

The joint-protective properties of glucosamine would make it an attractive therapeutic agent for arthritis except for two drawbacks: (i) the rate of response to glucosamine treatment is slower than for treatment with anti-inflammatory drugs, and (ii) glucosamine may fail to fulfill the expectation of degenerative remission. In studies comparing glucosamine with nonsteroidal anti-inflammatory agents, for example, a double-blinded study comparing 1500 mg glucosamine sulfate per day with 1200 mg ibuprofen demonstrated that pain scores decreased faster during the first two weeks in the ibuprofen patients than in the glucosamine-treated patients. However, the reduction in pain scores continued throughout the trial period in

patients receiving glucosamine and the difference between the two groups turned significantly in favor of glucosamine by week eight (Lopes Vaz, A., *Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of osteoarthritis of the knee in outpatients*, 8 CURR. MED RES OPIN. 145-149 (1982)). Thus, glucosamine may relieve the pain and inflammation of arthritis at a slower rate than the available anti-inflammatory drugs.

Despite this, the currently available glucosamine formulations have not been formulated to optimally attack and alleviate the underlying causes of osteoarthritis and rheumatoid arthritis. Moreover, as with many commercially available products, the available formulations do not have a history of usage or controlled clinical testing which might ensure their safety and efficacy.

An ideal formulation for the normalization of cartilage metabolism or treatment of osteoarthritis would combine adequate chondroprotection with potent anti-inflammatory activity. The optimal formulation for arthritis should enhance the general joint rebuilding qualities offered by glucosamine and attenuate the inflammatory response without introducing any harmful side effects. The formulation should be inexpensively manufactured and comply with all governmental regulations.

It has now surprisingly been found that these objectives are achieved by combining glucosamine with one or more selected Chinese herbs. Accordingly, the present invention provides a herbal composition which comprises glucosamine and at least one herb selected from *Tripterygium wilfordii, Ligustrum lucidum* and *Erycibe schmidtii.*

Tripterygium wilfordii, Ligustrum lucidum and *Erycibe schmidtii* are Chinese herbs that have been used for their anti-inflammatory properties. However, *Tripterygium wilfordii* can be toxic when used in high amounts. It has surprisingly been found that, when incorporated into the herbal composition of the present invention, its anti-inflammatory effect is enhanced to the extent that it can be used at sufficiently low doses to avoid adverse side effects.

In a preferred aspect the herbal composition of the invention comprises glucosamine and each of *Tripterygium wilfordii, Ligustrum lucidum* and *Erycibe schmidtii*. In a more preferred aspect the herbal composition comprises synergistically effective amounts of the glucosamine and the or each said herb. The invention therefore also provides the use of

glucosamine as a synergist in a herbal composition which comprises at least one Chinese herb selected from *Tripterygium wilfordii, Ligustrum lucidum* and *Erycibe schmidtii*. The invention further provides the use of at least one Chinese herb selected from *Tripterygium wilfordii, Ligustrum lucidum* and *Erycibe schmidtii* as a synergist in a herbal composition which comprises glucosamine. In this latter embodiment the herbal composition preferably further comprises one or both of the other two said Chinese herbs.

The present invention also provides a pharmaceutical or veterinary composition that comprises a pharmaceutically or veterinarily effective amount of a herbal composition of the invention as defined above and a pharmaceutically or veterinarily acceptable carrier or diluent.

The invention further provides a dietary composition, such as a dietary supplement, which comprises a herbal composition of the invention as defined above and a dietetically acceptable carrier or diluent.

The present invention further provides a method of dietary supplementation which comprises the administration to a human or animal suffering symptoms of an ailment which involves the inflammation or degeneration of joint tissues, such as arthritis, a herbal composition of the invention as defined above and continuing such administration of the composition until said symptoms are reduced.

The present invention also provides the use of glucosamine and at least one herb selected from *Tripterygium wilfordii, Ligustrum lucidum* and *Erycibe schmidtii* in the manufacture of a medicament for the treatment of symptoms of an ailment which involves the inflammation or degeneration of joint tissues, such as arthritis. A human or animal patient may thus be treated by a method which comprises the administration thereto of a pharmaceutical or veterinary composition of the invention as defined above. The symptoms of arthritis and other joint ailments which involve inflammation and/or degeneration of joint tissues are thereby alleviated.

The present compositions enhance the synthesis of glucosaminoglycans and hyaluronic acid while reducing the inflammatory response, thereby promoting both the rebuilding and healing of affected joints.

In the accompanying drawing, Figure 1 provides a scheme which illustrates the cycle of tissue destruction and inflammation in osteoarthritis and how the components of the present formulation may modulate this cycle. According to the present invention, glucosamine can

diminish tissue destruction; *Ligustrum lucidum* can inhibit COX-2 enzyme activity; *Tripterygium wilfordii* can inhibit the expression of COX-2 mRNA; and *Erycibe schmidtii* can inhibit inflammation and relieve pain.

The herbal compositions of the present invention may be used in dietary supplements and pharmaceutical or veterinary formulations. The herb or herbs selected from *Tripterygium wilfordii*, *Ligustrum lucidum* and *Erycibe schmidtii* enhance the joint-rebuilding effect of the glucosamine without introducing any harmful side effects. The herb(s) also provide an anti-inflammatory and analgesic effect.

The glucosamine used in the herbal composition of the present invention may be in any suitable form such as glucosamine sulphate, glucosamine hydrochloride or N-acetyl glucosamine. It may be employed as a dry powder or as a solution or dispersion. Preferably the glucosamine is a pharmaceutical grade that is commercially available,. An example of such a product is available from PharmLine, 41 Bridge Street, Florida, New York, 10921. Pharmaceutical grade glucosamine is standardized to greater than 97% purity.

The herbs used in the herbal composition of the present invention may be employed in any suitable form, for instance as dried herb or as a herbal extract.

When dried herb is used it is preferably in pulverized form. In this embodiment the whole herb is typically dried and ground to a powder. The resulting powder of the or each herb is then conveniently mixed with powdered glucosamine to form a herbal composition of the invention in powder form. The powder can be administered directly, for instance by being dispersed in a liquid for human subjects to drink or by being mixed into animal feed for animals, for example cats, to consume. Alternatively the powder can be processed into any other conventional dosage form such as tablets, granules or capsules.

When a herbal extract is used the extract is prepared by any conventional technique known for the extraction of ingredients from botanical material. Suitable techniques include solvent extraction and supercritical fluid extraction with a liquefied gas such as carbon dioxide. If desired the resulting extract may be dried before being formulated into a herbal composition of the invention, for instance by spray-drying or by freeze-drying (lyophilisation). In that case the dried extract may be mixed with powdered glucosamine to form a powder for direct administration to human or animal subjects, for instance as described above. Alternatively the extract may be used directly without prior drying.

The herbs or herb extracts are combined with the glucosamine using any conventional technique that is suitable for ingredients of this type. When the herbs or herb extracts and the glucosamine are all in dry form they are conveniently mixed together, for instance by hand or by means of a mechanical mixer. A mixing procedure of this type may also be suitable if some, but not all, of the components of the herbal composition are in dry form.

When *Tripterygium wilfordii* extract is employed in extract form it is preferably a pharmaceutical grade extract that can be obtained commercially, for example, from the Institute of Medicinal Plant Development, Haiding District, Xibeiwang, Beijing 100094, China, a Chinese manufacturer. Pharmaceutical grade *Tripterygium wilfordii* extract manufactured in China is standardized for triptolide content of about 0.1 weight percent and contains the full spectrum of diterpenes found in the plant. The pharmaceutical grade extract must pass extensive safety and efficacy procedures. As employed in the practice of the invention, the extract has a minimum triptolide content of about 0.01 to 0.5 percent by weight. Preferably, the minimum triptolide content is about 0.1 percent by weight. It is thought that *Tripterygium wilfordii* acts by the mechanism depicted in Figure 1 to reduce the expression of cyclooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis.

When *Ligustrum lucidum* is employed in extract form it is preferably a pharmaceutical grade extract that can be obtained commercially, for example, from the Institute of Medicinal Plant Development, Haiding District, Xibeiwang, Beijing 100094, China, a Chinese manufacturer. The pharmaceutical grade extract must pass extensive safety and efficacy procedures. Pharmaceutical grade *Ligustrum lucidum* extract manufactured in China is standardized for oleanolic acid content of about 45 percent by weight. The *Ligustrum lucidum* extract used for the present invention preferably has an oleanolic acid content of about 30 to about 70 weight percent, and contains additional triterpenoids such as ursolic acid. More preferably, the extract used for the present compositions and methods has a minimum oleanolic acid content of about 45 percent by weight.

It is though that the action of the *Ligustrum lucidum* is to inhibit COX-2 enzyme activity by the mechanism shown in Figure 1. *Ligustrum lucidum*, contains triterpenes oleanolic and ursolic acids which may provide the anti-inflammatory activity. *Ligustrum lucidum* can also provide hepatoprotection, antitumor promotion, antihyperlipidemia, antihyperglycemia, and protection against aspirin-induced ulcers.

When *Erycibe schmidtii* is employed in extract form it is preferably a pharmaceutical grade extract that can be obtained commercially, for example, from the Institute of Medicinal Plant Development, Haiding District, Xibeiwang, Beijing 100094, China, a Chinese manufacturer. The pharmaceutical grade extract must pass extensive safety and efficacy procedures. Pharmaceutical grade *Erycibe schmidtii* extract manufactured in China is standardized for scopoletin content of about 0.35 weight percent. Preferably, for use in the composition of this invention the extract has a scopoletin content of about 0.25 to about 0.70 percentage by weight. More preferably the extract has a minimum scopoletin content of about 0.35 percent by weight.

Erycibe schmidtii (Ding Gon Teng) is the major ingredient herb (92% by weight) of the medicated wine called "*Feng Liao Xing Feng Shi Die Da Yao Jiu*" or "Ding Gong Teng Feng Shi Yao Jiu" (DGT wine). The main chemical ingredients of *E. schmidtii* include scopoletin (the aglycone) and scopolin (the glycoside) which is thought to be responsible for the anti-inflammatory and analgesic activity of the herb.

The herbal composition of the present invention as described above is typically formulated into a pharmaceutical or veterinary composition or a dietary composition such as a dietary supplement, by a conventional method. In addition to the glucosamine and the herbs, such compositions may include pharmaceutically, veterinarily or dietetically acceptable carriers or diluents as well as various additives such as other vitamins and minerals and inert ingredients such as talc and magnesium stearate that are standard excipients in the manufacture of tablets, capsules or other dosage forms. The finished pharmaceutical or veterinary dosage form may be formulated for any route of administration such as orally, parenterally or topically.

The pharmaceutically, veterinarily or dietetically acceptable carrier or diluent may be, for example, a solvent, dispersion medium, coating, isotonic or absorption delaying agent, sweetener or the like. The carrier may be prepared from a wide range of materials including, but not limited to, diluents, binders and adhesives, lubricants, disintegrants, coloring agents, bulking agents, flavoring agents, sweetening agents and miscellaneous materials such as buffers and adsorbents that may be needed in order to prepare a particular composition. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient,

its use in the present compositions is contemplated.

In one embodiment, talc and magnesium stearate are included in the dietary compositions and/or pharmaceutical compositions of the present invention. When these components are added they are preferably the Astac Brand 400 USP talc powder and the veritable grade of magnesium stearate. Other ingredients to improve the manufacture of this composition as a dietary bar, functional food or pharmaceutical formulation include flavorings, sugars, proteins and/or modified starches, as well as fats and oils.

The dietary compositions and pharmaceutical and veterinary compositions of the present invention can be formulated into a finished dosage form in any suitable manner known to one of skill in the art. The daily dosage takes account of factors such as the age, weight and condition of the patient to be treated. A typical daily dosage is about 1500 mg of glucosamine for a human divided into one to three tablets, capsules or chewable bars. Using the standard estimate of body weight for an individual as 70 kg, the daily dose of glucosamine per kg of body weight is approximately 21 mg/kg-day.

In one embodiment the herbal composition of the invention, for instance in the form of a dietary supplement or pharmaceutical composition, is formulated into a capsule or tablet using techniques available to one of skill in the art. In capsule or tablet form the recommended daily dose for an adult human or animal would preferably be one to six capsules or tablets. However, the present compositions may also be formulated in any other convenient form, such as an injectable solution or suspension, a spray solution or suspension, a lotion, a gum, a lozenge, a food or snack item. Food, snack, gum or lozenge items can include any ingestable ingredient, including sweeteners, flavorings, oils, starches, proteins, fruits or fruit extracts, vegetables or vegetable extracts, grains, animal fats or proteins. Thus, the present herbal compositions can be formulated into food products such as cereals, snack items such as chips, bars, gum drops, chewable candies or slowly dissolving lozenges.

The herbal composition of the present invention is also suitably formulated into granules or a powder. In this form it can be readily dispersed in water or other liquid such as tea or a soft drink for human subjects to drink. It can be equally readily mixed into feed for administration to animals such as cattle, cats and dogs.

The herbal composition of the present invention is administered in an amount sufficient to relieve the symptoms of degenerative joint disease, joint inflammation or arthritis

while minimizing adverse side effects. In one embodiment, a therapeutically effective amount is an amount sufficient to enhance the synthesis of glucosaminoglycans and hyaluronic acid without causing harmful side effects. In another embodiment, a therapeutically effective amount of the composition is an amount sufficient to reduce the expression or activity of cyclooxygenase-2 without causing harmful side effects. In yet another embodiment, the therapeutically effective amount is an amount sufficient to reduce the inflammatory response without causing harmful side effects.

Preferably, a herbal composition of the present dietary invention is formulated to deliver each component in the following amounts:

(a) about 15.0 to 25.0 mg glucosamine per kg body weight;

(b) about 0.25 to 5.0 mg *Tripterygium wilfordii* per kg body weight;

(c) about 2.5 to 10.0 mg/kg *Ligustrum lucidum* per kg body weight; and

(d) about 2.5 to 10.0 mg *Erycibe schmidtii* per kg body weight.

In a preferred embodiment the herbal composition of the present invention is formulated to deliver each component in the following amounts:

a. about 21 mg pharmaceutical grade glucosamine per kg body weight;

b. about 1.5 mg *Tripterygium wilfordii* per kg body weight;

c. about 5,0 mg *Ligustrum lucidum* per kg body weight; and

d. about 6.5 mg *Erycibe schmidtii* per kg body weight.

The invention will be further described in the following Examples.

EXAMPLE 1: Preparation of Herbal Composition

A herbal composition of the invention was prepared containing pharmaceutical grade glucosamine, *Tripterygium wilfordii*, *Ligustrum lucidum* and *Erycibe schmidtii*. The pharmaceutical grade glucosamine, which is standardised to contain no less than 97% glucosamine calculated as glucosamine sulphate, was purchased from PharmLine, USA. The three herb extracts were made at the Institute of Medicinal Plant Development, Beijing, China.

The authentication and quality evaluation of the raw herb material, critical to the production of the standardised herb extracts and the therapeutic effect of the finished product, were achieved by conventional macroscopic and microscopic methods of inspection and

authentication involving the application of pharmacognosy, phytochemistry and Chinese Materia Medica. In addition TLC and HPLC profiling were used.

The herb extracts of *Tripterygium wilfordii, Ligustrum lucidum* and *Erycibe schmidtii* were made separately using extraction procedures designed specifically for each herb in order to achieve the expected therapeutic potency of the extracts. With the consistent concentration of 10:1 (1 g extract is equivalent to 10 g dry herb), each extract contained a set amount of selected chemical markers which could be quantified by HPLC. The chemical marker contents was 0.1% triptolide in *Tripterygium wilfordii* extract, 45% oleanolic acid in *Ligustrum lucidum* extract and 0.35% scopoletin in *Erycibe schmidtii* extract. Each extract was standardized.

The pharmaceutical grade glucosamine was combined with the herb extracts in a defined proportion of each ingredient of *Tripterygium wilfordii, Ligustrum lucidum* and *Erycibe schmidtii* to form a herbal composition.

EXAMPLE 2: Preparation of Pharmaceutical Composition

A phamaceutical composition in tablet dosage form was prepared by formulating the herbal composition prepared according to Example 1 with such tabletting excipients as talc and magnesium stearate such that the following amounts of active ingredients could be delivered per kg body weight per day:

(a) 21 mg/kg glucosamine (b) 1.5 mg/kg *Tripterygium wilfordii* extract (0.1 % wt triptolide); (c) 5.0 mg/kg *Ligustrum lucidum* extract (45% wt oleanolic acid); and (d) 6.5 mg/kg *Erycibe schmidtii* extract (0.35% wt scopoletin).

Initial testing of the finished dosage form revealed an improvement in clinical signs due to osteoarthritis following seven to ten doses of the pharmaceutically formulation.. Additionally, it seemed that continued rebuilding of the affected joints could be expected to occur throughout the period of treatment rather than mere attenuation of clinical pathology. This result would be expected in all mammals affected by osteoarthritis.

EXAMPLE 3: Clinical evaluation in the dog

1. In a clinical study on dogs, the tablet dosage form described in Example 2 was administered daily to a group of dogs (1 tablet per day) observed to be suffering from symptoms of arthritis. Preliminary observations by a veterinarian after a week to ten days indicated that there was an improvement in each animal's condition.

2. An 11 year old female long haired miniature Dachshund ("Clover") was diagnosed as suffering from arthritis in her back (fusion of the vertebrae). Clinical symptoms included difficulties with walking and with ascending and descending stairs; lethargy; and crying due to pain. She had been receiving painkillers prescribed by her vet.

After two weeks of administration of the tablet dosage form described in Example 2 (1 tablet per day) Clover's movement had greatly improved and four weeks of the treatment regimen resulted in the disappearance of most of her symptoms. Subsequently she could freely walk up and down stairs showing no signs of pain and no longer required painkillers. During the treatment no additional painkiller was administered to Clover.

CLAIMS

1. A herbal composition which comprises glucosamine and at least one herb selected from *Tripterygium wilfordii*, *Ligustrum lucidum* and *Erycibe schmidtii*.

2. A herbal composition according to claim 1 which comprises glucosamine, *Tripterygium wilfordii*, *Ligustrum lucidum* and *Erycibe schmidtii*.

3. A herbal composition according to claim 1 or 2 which comprises synergistically effective amounts of the glucosamine and the or each said herb.

4. A herbal composition according to any one of the preceding claims which is formulated to deliver each component in the following amounts:

a. from 15.0 to 25.0 mg glucosamine per kg body weight;
b. from 0.25 to 5.0 mg *Tripterygium wilfordii* per kg body weight;
c. from 2.5 to 10.0 mg *Ligustrum lucidum* per kg body weight; and
d. from 2.5 to 10.0 mg *Erycibe schmidtii* per kg body weight.

5. A herbal composition according to any one of the preceding claims which is formulated to deliver each component in the following amounts:

a. about 21 mg pharmaceutical grade glucosamine per kg body weight;
b. about 1.5 mg *Tripterygium wilfordii* per kg body weight;
c. about 5.0 mg *Ligustrum lucidum* per kg body weight; and
d. about 6.5 mg *Erycibe schmidtii* per kg body weight.

6. A herbal composition according to any one of the preceding claims wherein the glucosamine is selected from glucosamine sulphate, glucosamine hydrochloride and N-acetyl glucosamine.

7. A herbal composition according to any one of the preceding claims wherein the *Tripterygium wilfordii* contains at least about 0.1% wt triptolide.

8. A herbal composition according to any one of the preceding claims wherein the *Ligustrum lucidum* contains at least about 45% wt oleanolic acid.

9. A herbal composition according to any one of the preceding claims wherein the *Erycibe schmidtii* contains at least about 0.35% wt scopoletin.

10. A herbal composition according to any one of the preceding claims which further comprises one or more vitamins or minerals.

11. A herbal composition according to any one of the preceding claims which further comprises one or more proteins, fats or carbohydrates.

12. A dietary composition comprising a herbal composition as claimed in any one of claims 1 to 11 and a dietetically acceptable carrier or diluent.

13. A pharmaceutical or veterinary composition comprising a pharmaceutically or veterinarily effective amount of a herbal composition as claimed in any one of claims 1 to 11 and a pharmaceutically or veterinarily acceptable carrier or diluent

14. A composition according to any one of claims 1 to 13 which is formulated in capsule form.

15. A composition according to any one of claims 1 to 13 which is formulated in tablet form.

16. A composition according to any one of claims 1 to 13 which is formulated in bar form.

17. A composition according to any one of claims 1 to 13 which is formulated as a chewable gum.

18. A composition according to any one of claims 1 to 13 which is formulated as a lotion.

19. A composition according to any one of claims 1 to 13 which is formulated as a powder or as granules.

20. A composition according to any one of claims 1 to 13 which is formulated as an injectable solution or suspension.

21. A food product which includes a composition as claimed in any one of claims 1 to 11.

22. A food product according to claim 21 wherein said food is cereal.

23 A method of dietary supplementation which comprises administering to a human or animal suffering symptoms of an ailment that involves the inflammation or degeneration of joint tissues a composition as claimed in any one of claims 1 to 12 and continuing said administering of the composition until said symptoms are reduced.

24. A method according to claim 23 wherein said animal is a mammal selected from dogs, cats, horses and cattle.

25. Use of glucosamine and at least one herb selected from *Tripterygium wilfordii*, *Ligustrum lucidum* and *Erycibe schmidtii* in the manufacture of a medicament for the treatment of an ailment that involves the inflammation or degeneration of joint tissues..

26. Use of glucosamine, *Tripterygium wilfordii*, *Ligustrum lucidum* and *Erycibe schmidtii* in the manufacture of a medicament for the treatment of an ailment that involves the inflammation or degeneration of joint tissues.

27. Use according to claim 25 or 26 wherein the ailment is arthritis.

28. Use according to any one of claims 25 or 27 wherein the glucosamine and the or each said herb are used in synergistically effective amounts.

29. Use according to any one of claims 25 to 28 wherein the medicament is for oral, parenteral or topical administration.

30. Use according to any one of claims 25 to 28 wherein said ailment is rheumatoid arthritis.

31. Use according to any one of claims 25 to 29 wherein said ailment is osteoarthritis.

32. A method of treating arthritis which comprises administering to a human or animal patient in need thereof a pharmaceutical or veterinary composition as claimed in claim 13.

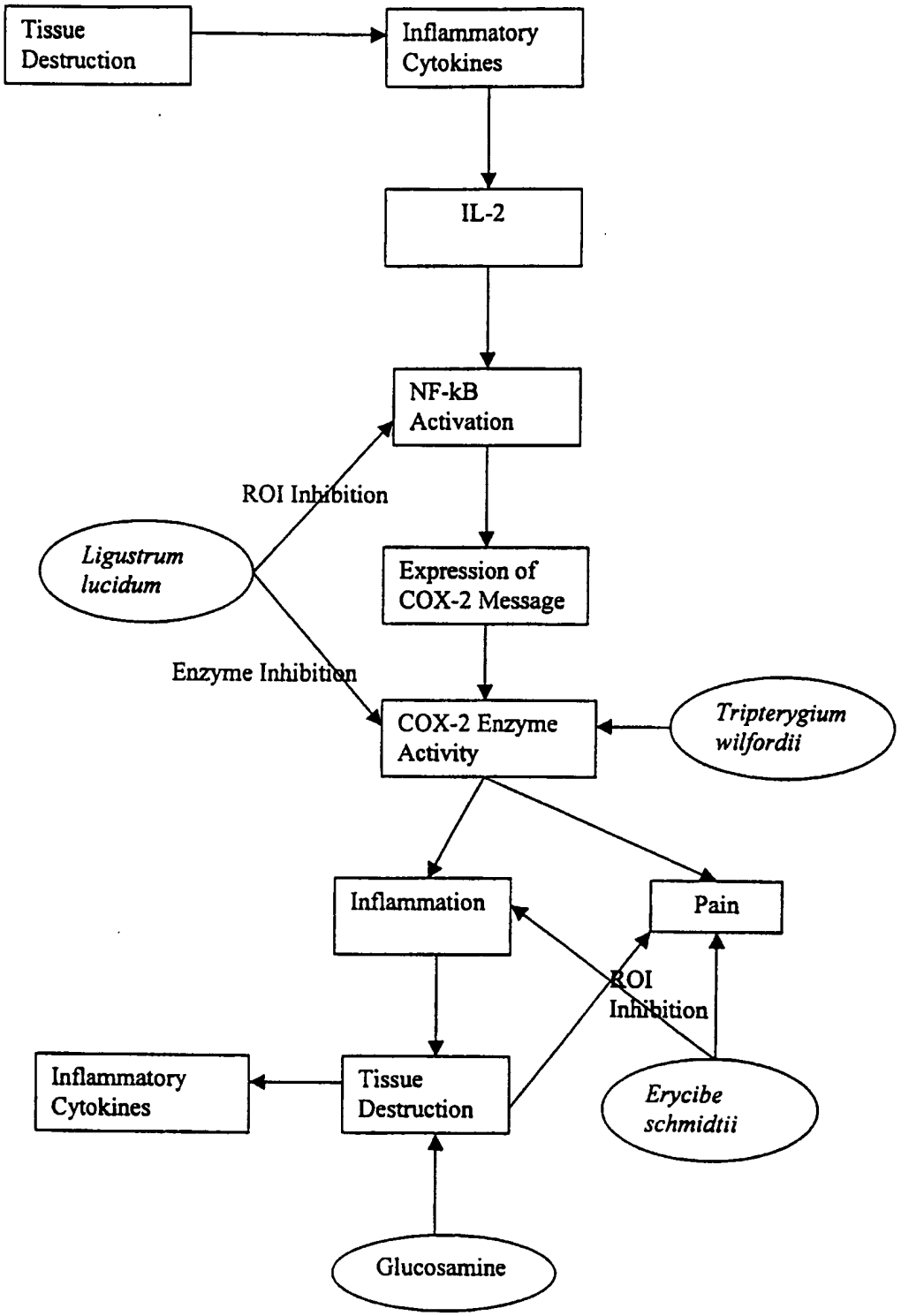
Tissue Destruction
Inflammatory Cytokines
IL-2
NF-kB Activation
ROI Inhibition
Ligustrum lucidum
Expression of COX-2 Message
Enzyme Inhibition
COX-2 Enzyme Activity
Tripterygium wilfordii
Inflammation
Pain
ROI Inhibition
Inflammatory Cytokines
Tissue Destruction
Erycibe schmidtii
Glucosamine

Fig. 1

INTERNATIONAL SEARCH REPORT

Interna al Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61K31/70 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 51302 A (UNIV WASHINGTON) 19 November 1998 (1998-11-19) page 4, line 7-12; claim 6; examples 1,3,4,10	1-32
E	WO 00 30666 A (UNIV WASHINGTON) 2 June 2000 (2000-06-02) page 4, line 22-26; examples 1,3,4	1-32
E	WO 00 33659 A (UNIV WASHINGTON) 15 June 2000 (2000-06-15) page 4, line 18-25 page 11, line 16-28; examples 1,3,4	1-32

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2000	15/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 59578 A (RES DEV FOUNDATION) 25 November 1999 (1999-11-25) page 11, line 20-25 page 13, line 5-15 page 81; claims 13,14,68-70,80-87; figures 36-40	1-32
P,X	WO 00 12483 A (PHARMAGENESIS INC ;MUSSER JOHN H (US)) 9 March 2000 (2000-03-09) abstract; claim 1 page 5, line 1-5	1-32
Y	WO 98 13057 A (CAI JIM ;OLSEN NANCY J (US); TAO XE LIEN (US); LIPSKY PETER E (US)) 2 April 1998 (1998-04-02) claims 3,4; examples 3,4,9,17,19,21	1-32
P,Y	US 5 972 998 A (WICKRAMARATNE MAHINDA ET AL) 26 October 1999 (1999-10-26) claims 29,32,35; example 25	1-32
Y	EP 0 852 946 A (PAOLI AMBROSI GIANFRANCO DE) 15 July 1998 (1998-07-15) page 4, line 10-15; claims 8,10; examples 4,5	1-32
X,P	CONN D. L. ET AL: "Alternative treatments and rheumatic diseases" BULLETIN ON THE RHEUMATIC DISEASES, vol. 48, no. 7, November 1999 (1999-11), pages 1-4, XP000961321 page 1, column 1 page 3, column 1	1-32
P,X	RAMGOLAM, V. ET AL: "Traditional chinese medicines as immunosuppresive agents" ANNALS ACADEMY OF MEDICINE, SINGAPORE, vol. 29, no. 1, January 2000 (2000-01), pages 11-16, XP000961356 abstract page 12, column 2 -page 13, column 1	1-32
P,Y	TAO X. ET AL.: "The chinese antiinflammatory and immunosuppressive herbal remedy Tripterygium Wilfordii Hook F." REUMATHIC DISEASE CLINICS OF NORTH AMERICA, vol. 26, no. 1, February 2000 (2000-02), pages 29-50, XP000961355 abstract; figure 1; table 1 page 34 -page 38	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 00/02092

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9851302 A	19-11-1998	AU 7580098 A	08-12-1998
		EP 1019044 A	19-07-2000
WO 0030666 A	02-06-2000	AU 1633500 A	13-06-2000
WO 0033659 A	15-06-2000	AU 3113500 A	26-06-2000
WO 9959578 A	25-11-1999	AU 4087199 A	06-12-1999
WO 0012483 A	09-03-2000	AU 6242599 A	21-03-2000
WO 9813057 A	02-04-1998	AU 7377196 A	17-04-1998
		EP 1007066 A	14-06-2000
US 5972998 A	26-10-1999	NONE	
EP 0852946 A	15-07-1998	IT BS960094 A	29-05-1998
		CA 2219849 A	29-05-1998